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SYNCHRONIZED PULSATILE  
EXTRACORPOREAL CORONARY PERFUSION:  
ITS EFFECTS ON PRESERVATION OF  
LEFT VENTRICULAR FUNCTION IN THE  
BEATING NONWORKING CANINE HEART.

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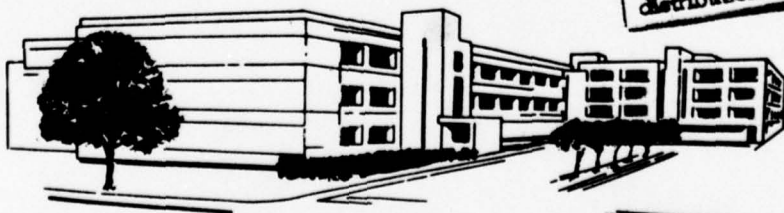
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The results of this study suggest that in the beating nonworking canine heart synchronized pulsatile perfusion offers no advantage over standard continuous cardiopulmonary perfusion.

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#### ABSTRACT

Twelve mongrel dogs were divided into two groups and subjected to either continuous or synchronized pulsatile cardiopulmonary bypass. Left ventricular function was evaluated with measurements of stroke volume, stroke work, and  $dp/dt$  maximum. Although slight reductions were noted in the values for stroke volume and stroke work following two hours of left ventricular bypass in both groups, no significant effects attributable to perfusion modality were noted. The results of this study suggest that in the beating nonworking canine heart synchronized pulsatile perfusion offers no advantage over standard continuous cardiopulmonary perfusion.

## PREFACE

This institute report represents the initial work completed on the work unit entitled "Studies in Pulsatile Extracorporeal Perfusion" at Letterman Army Institute of Research. This work represents utilization of techniques and equipment that have subsequently been improved; therefore, this report constitutes primarily a "pilot study." The conclusions reached in this study have been confirmed in swine, a more developed animal model. Reports on the later studies are available in the indexed literature (Ann Thorac Surg 24:582, 1977; Surg Forum 28:262, 1977; Fed Proc 36:599, 1977). We are reporting this earlier work as an institute report for the purpose of providing full documentation of the work unit and to establish an accessible reference for other work which will be submitted to the open literature.

We acknowledge gratefully the valuable assistance of Douglas M. Behrendt, M.D., Kenneth E. Jochim, Ph.D., and William W. Parmley, M.D. in the designing of this animal model.

John V. Tyberg, M.D., Ph.D., is Assistant Professor of Medicine and is affiliated with the University of California, San Francisco. Dr. Moores, the senior investigator, is currently affiliated with the Department of Surgery, University of California, San Diego.

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## INTRODUCTION

Most clinical extracorporeal perfusion is nonpulsatile because of its technical simplicity and its maintenance of near-normal body function during short periods of bypass (1-4). With the possible need for long-term life support, new interest has emerged in the importance of pulsatile flow. Total body perfusion and individual organ studies generally have shown the beneficial effects of pulsatile perfusion; such effects include decreased peripheral resistance, improved microcirculation, increased oxygen consumption, and increased urine production (5-9).

The comparative effects of pulsatile and nonpulsatile perfusion on myocardial function have received relatively little attention. Pulsatile perfusion may afford some benefit to the fibrillating heart (10,11), but its importance to the beating heart remains unknown. It was to this question that the present study was directed.

## METHODS

### Experimental Design

Twelve adult mongrel dogs (weight, 25-32 kg) were sequentially assigned to two groups, one to receive pulsatile and the other continuous perfusion. Each animal was surgically prepared for myocardial performance assessment, as described below, during an initial one-hour period of continuous perfusion. At the end of the period, control values were obtained. Thereafter, the animal was perfused for an additional two hours in either a continuous or pulsatile mode, and at the end of this period, test values were obtained.

The dogs were anesthetized with intravenous (IV) thiamylal sodium (20 mg/kg). The anesthetic state was maintained with IV meperidine hydrochloride (1.5 mg/kg) and a succinylcholine chloride drip

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(approximately 20 mg/hr) given at approximately one-hour intervals. Mechanical ventilation with intratracheal intubation and 100% oxygen was maintained throughout the experiment.

All animals were placed on total heart bypass (Figure 1) and a mean arterial pressure of 100 mm Hg was maintained. Test perfusion utilized aortic cannulation with left ventricular venting. All perfusions were carried out with a Sarns heart assist pump as previously described (12). This pump utilizes a roller head modified to deliver pulsatile flow synchronized with the patient's electrocardiogram. Silastic<sup>R</sup> tubing (5/8 inch internal diameter, Dow-Corning, Midland, Michigan) was used in the pump head for both the continuous and pulsatile runs. The pump was primed with fresh canine blood and lactated Ringer solution to provide a hemoglobin concentration of approximately 10 gm/dl. For the pulsatile runs, the pump was adjusted to deliver a pulse pressure of 60 mm Hg during diastole with a mean arterial pressure of 100 mm Hg.

After subtotal excision of the right atrium, heart rate was controlled in all animals at 110 bpm by left atrial pacing. A catheter was also placed in the coronary sinus; sinus drainage was collected and measured in a graduated cylinder. Left ventricular pressure was measured with an indwelling transducer (Model P-13, Konigsberg Instruments, Inc., Pasadena, California). Superior vena cava and aortic pressures were measured by using indwelling catheters connected to Clark pressure transducers (Bell and Howell), and recorded on a physiologic recorder (Model DR-8, Electronics for Medicine, Inc., White Plains, New York). Cardiac output was determined by the flow from the previously calibrated Sarns pump during both total and right heart bypass.

The stroke volume, stroke work, and dp/dt maximum values were derived from left ventricular function curves obtained during right heart bypass without ventricular venting. Approximately five minutes of by-pass were required to construct these function curves. For the purposes of comparison, values for stroke volume, stroke work, and mean arterial pressure were taken at a left ventricular end diastolic pressure of 6 mm Hg, while values for dp/dt maximum were taken at a mean arterial pressure of 100 mm Hg. Stroke volume was obtained by dividing pump output by heart rate. Stroke work was calculated from stroke volume and mean ventricular pressure during ejection according to the following equation:

$$\text{Stroke Work} = (\text{S.V.}) (\bar{P}_v) (1.35 \times 10^{-3})$$

where, S.V. = stroke volume in ml,  $\bar{P}_v$  = mean ventricular pressure during ejection, and  $1.35 \times 10^{-3}$  is a constant. Work is expressed as gm-M.

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12. Moores, W.Y., et al. Ann Thorac Surg 12:262, 1971



Peripheral resistance was calculated according to the following formula:

$$\text{Resistance} = \frac{(\bar{P}_a) \times (1332)}{Q}$$

where,  $\bar{P}_a$  = mean arterial pressure in mm Hg,  $Q$  = pump output in ml/sec, and 1332 is a constant. Resistance values are expressed as dyne sec-cm<sup>-5</sup>.

Arterial, mixed venous, and coronary sinus oxygen saturations were measured with an oximeter (American Optical, Buffalo, New York), and the hemoglobin concentration (Hgb) was measured with a hemoglobino-meter (Coulter Electronics, Hialeah, Florida). The hemoglobin O<sub>2</sub> content of the blood was calculated according to the following equation:

$$\text{Hemoglobin O}_2 \text{ content} = \frac{\text{Hgb (gm/dl)} \times 1.34 \times \text{O}_2 \text{ saturation}}{100}$$

Myocardial oxygen consumption in the nonworking heart was calculated as the product of coronary sinus flow collected during total bypass and the arterial coronary sinus difference in hemoglobin oxygen content. Total body oxygen consumption was obtained in a similar fashion by using the arterial venous hemoglobin oxygen content difference and total pump output.

Pyruvate and lactate determinations were performed according to the technique of Beutler (13), and myocardial lactate extraction (%) was expressed as:

$$\text{Lactate extraction} = \frac{(L_a) - (L_{cs})}{(L_a)} \times 100$$

where,  $(L_a)$  = arterial lactate concentration and  $(L_{cs})$  = coronary sinus lactate concentration.

Following the three-hour period of perfusion, each animal was sacrificed and the myocardium was excised for histologic evaluation of damage.

#### Statistical Analysis

The data were evaluated by using a standard Student's "t" test or a two factor analysis of variance with one repeated measure for group (pulsatile versus continuous) and treatment (control versus test) effects. In addition, Pearson correlation coefficients were obtained between all variables. The latter procedure was carried out by the Generalized Research Analysis Statistical System (GRASS) implemented on a CDC-7600 computer (Lawrence Berkeley Laboratory Computing Center, University of California, Berkeley, California).

13. Beutler, E. Red Cell Metabolism: A Manual of Biochemical Methods. New York: Grune and Stratton, 1971, pp 108-111

## RESULTS

Both groups of animals were similar in terms of weight and hemoglobin concentration (Table 1) during control and test perfusion periods. Routine control of ventilation and bicarbonate administration were used to maintain the arterial pH as close as possible to normal; despite these efforts, however, the continuous perfusion group did have a lower pH value during the control period ( $p < 0.05$ ) and a lower oxygen tension ( $p < 0.05$ ).

The hemodynamic results are summarized in Table 2. Values are given for the control and test periods for both continuous and pulsatile perfusion. Both groups showed decrements in stroke volume and stroke work during the test period. These treatment effects were statistically significant ( $p < 0.05$ ) overall, i.e., independent of grouping. They were not significant, however, when each group was evaluated independently. Other apparent within- and between-group differences were likewise insignificant, statistically. Nevertheless, within-group comparisons suggest a slightly greater decrease in stroke volume, expressed as percent of control, in the pulsatile perfusion group (83% of control) than in the continuous perfusion group (90% of control). Reductions in stroke work were more comparable in both groups (continuous, 73% of control; pulsatile, 78% of control), with slightly less reduction in the pulsatile group. Analysis of  $dp/dt$  maximum revealed little change in either group (continuous, 101% of control; pulsatile, 95% of control), although there was some suggestion for lower values overall in the pulsatile group. Mean arterial pressure/left ventricular end diastolic pressure relationships would be expected to affect stroke volume, stroke work, and  $dp/dt$  maximum values as indices of contractility. These relationships, however, were stable within both groups. Mean arterial pressure, at a left ventricular end diastolic pressure of 6 mm Hg, was approximately 100 mm Hg in the continuous perfusion group and 90 mm Hg in the pulsatile perfusion group. Again, the mean differences in the hemodynamic determinations were not statistically significant.

Values for coronary flow, arteriovenous oxygen difference, oxygen consumption, and lactate extraction are summarized in Table 3. Again, no statistically significant differences attributable to perfusion mode were observed. A slight decrease in coronary flow of equal magnitude in each group was noted. Following the test period, oxygen consumption and arterial-venous oxygen saturation differences were less with pulsatile perfusion than with continuous perfusion. This decrease in oxygen consumption following pulsatile perfusion was also accompanied by an increase in lactate extraction (21% versus 9%).

Values for total body oxygen consumption, venous lactate, pyruvate, and peripheral resistance are summarized in Table 4. Both groups showed increases in venous lactate levels and lactate:pyruvate ratios following the test perfusion, but again, the large variation between animals

seemed to preclude the appearance of any statistically significant between-group differences. The data were also examined as percent differences to avoid weight variation; no additional significance was noted. Small, statistically insignificant differences in mean peripheral resistance were noted, with a slight increase in the pulsatile group and a slight decrease in the continuous group. Total body oxygen consumption decreased slightly, but insignificantly, in the continuous perfusion group and increased slightly in the pulsatile perfusion group.

Peripheral resistance changes in individual animals are diagrammed in Figure 2. Despite the lack of statistically significant differences, there is a slight trend for most animals in the continuous perfusion group to maintain or decrease their peripheral resistance during the test perfusion, and for most animals to increase their resistance during the similar period in the pulsatile perfusion group.

Light microscopic examination of myocardial tissue from both groups showed some vascular ectasia, subepicardial and subendocardial hemorrhage, and some passive congestion. No differences attributable to perfusion modality were apparent.

#### DISCUSSION

This study attempted to determine whether or not synchronized pulsatile perfusion would provide improved support of the myocardium during extracorporeal circulation. No advantage with pulsatile perfusion was noted. The main thrust of the study was concerned with measurements of contractility as expressed in changes of stroke volume, stroke work, and  $dp/dt$  maximum. Statistically insignificant decreases were noted in the mean values for stroke volume ( $p>0.5$ ) and stroke work ( $p>0.3$ ) in both groups, with no advantage seen with pulsatile perfusion. We found no difference in  $dp/dt$  maximum determinations between groups ( $p>0.5$ ). In evaluating contractility measurements based on stroke volume, stroke work, and  $dp/dt$  maximum measurements, both pre-load and after-load conditions have to be specified carefully. No artificial control of mean arterial pressure was imposed in this study in an attempt to preserve reflex peripheral cardiovascular effects that would be involved in a clinical perfusion. In general, no major change in mean left ventricular end diastolic pressure/mean arterial pressure relationships was observed (Table 2).

Therefore, it seems reasonable to conclude that three hours of extracorporeal support of the beating nonworking myocardium does not result in a major impairment of performance, at least in terms of lost contractility, regardless of the type of perfusion. This finding is consistent with the findings of Nelson et al (14), who report no

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14. Nelson, R.L., et al. Surg Forum 26:261, 1975



decrease in left ventricular function in a group of dogs submitted to three hours of continuous flow cardiopulmonary bypass. A slight drop in mean coronary flow (approximately 10% in both groups) was noted in the present study. Presumably, therefore, the augmentation of diastolic filling associated with synchronized pulsatile perfusion did not lead to an augmented flow. It might be noted, however, that only coronary sinus flow was measured, and it is possible that thebesian vein drainage (unmeasured) may have increased.

During the course of perfusion, a decrease in myocardial oxygen consumption was noted in the pulsatile perfusion group. This occurred with a concomitant increase in myocardial lactate extraction. A high lactate extraction would seem to indicate adequate oxygen delivery to support aerobic metabolism. Thus, the decreased oxygen consumption may reflect a decreased oxygen requirement during pulsatile support. Since the variation is large and the differences are not statistically significant, this possible benefit of pulsatile perfusion remains speculative.

We noted a slightly higher total body peripheral vascular resistance in the pulsatile perfusion group and a slight decrease in total body oxygen consumption in the continuous perfusion group. These effects were not statistically significant and, as a consequence, the differences and mean values must be interpreted with caution. The failure of this study to substantiate the findings of decreased resistance and significantly increased oxygen consumption with pulsatile support reported by other investigators (15,16) may be attributed to the nature of our preparation. It required an initial one-hour period of continuous perfusion to complete the preparation for controlled left ventricular measurements. Perhaps a study which has a less complex and less controlled preparation would allow the collection of control measurements prior to any period of extracorporeal perfusion.

#### CONCLUSIONS

On the basis of the data reported here, it would seem fair to conclude that synchronized pulsatile perfusion offers little functional benefit over continuous perfusion in the beating nonworking heart. Since the heart is unique in receiving its perfusion primarily during the diastolic phase, it is providing its own pulsatile perfusion, even with continuous aortic root pressure. Thus, the additional diastolic augmentation from the pump may provide only marginal benefit.

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## RECOMMENDATIONS

We recognize the deficiencies of this portion of our investigation on pulsatile extracorporeal perfusion, and so we initiated further work to validate (or modify) the conclusions. The functional measurements require stricter control of afterload (here specified as mean arterial pressure) and refinements in the operative preparation that would allow a closer approximation of test values to control values, if the heart is truly not being damaged by continuous or pulsatile flow while empty and beating. Furthermore, additional studies need to be done to determine the response of the heart to these interventions when volume loaded or during fibrillation. Although the preparation is rather complex, additional valuable information could be achieved by the addition of flow distribution investigations using radiolabelled microspheres. This study and the additional studies mentioned up to this point are in the normal heart. To evaluate fully the role of pulsatile perfusion, investigations should be conducted on hearts compromised by such factors as hypotension ("shock"), anemia, ischemia, hypoxia, and possible drug utilization.

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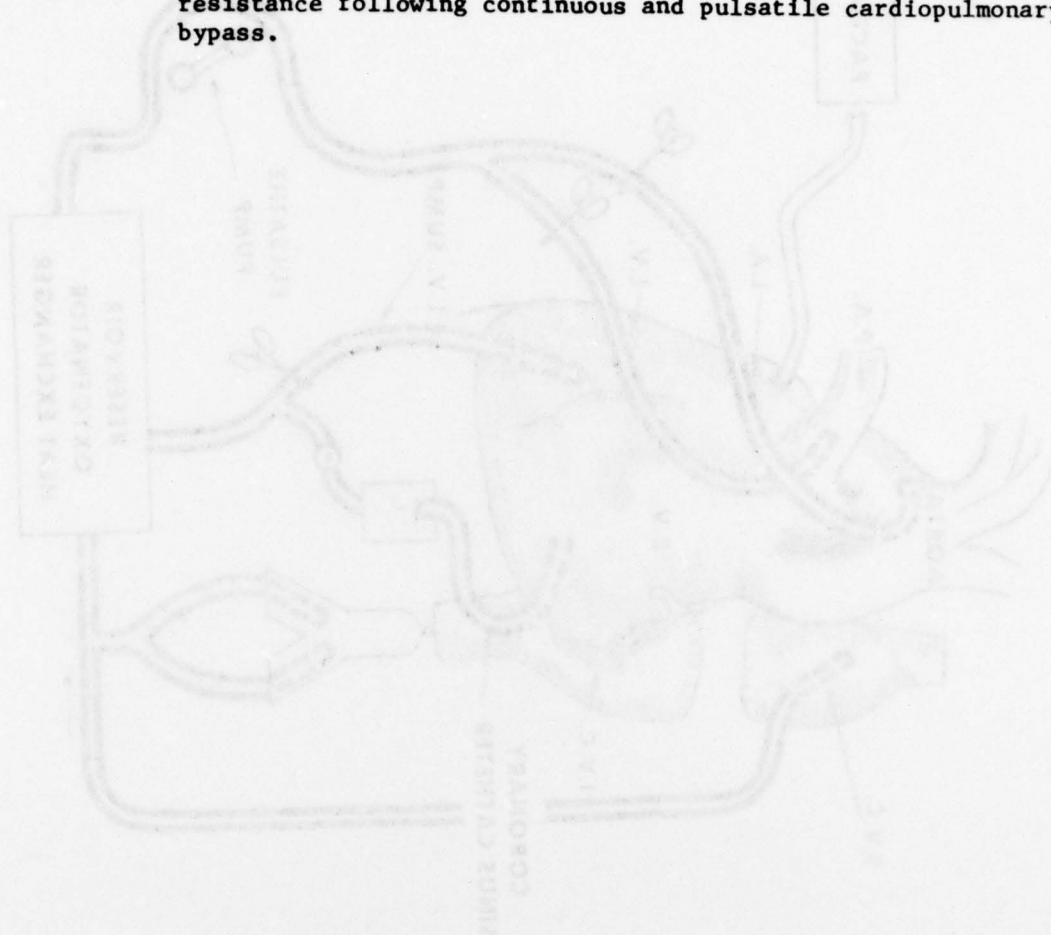
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# LEGENDS OF FIGURES

Figure 1. Diagram illustrating the surgical preparation for total and right heart bypass. (S.V.C., superior vena cava; P.A., pulmonary artery; L.A., left atrium; L.V., left ventricle; R.V., right ventricle; I.V.C., inferior vena cava.) Coronary sinus drainage is initially collected in a graduated cylinder prior to being returned to the circulation.

Figure 2. Grafts illustrate individual animal variation in peripheral resistance following continuous and pulsatile cardiopulmonary bypass.



APPENDIX A



FIGURE 1

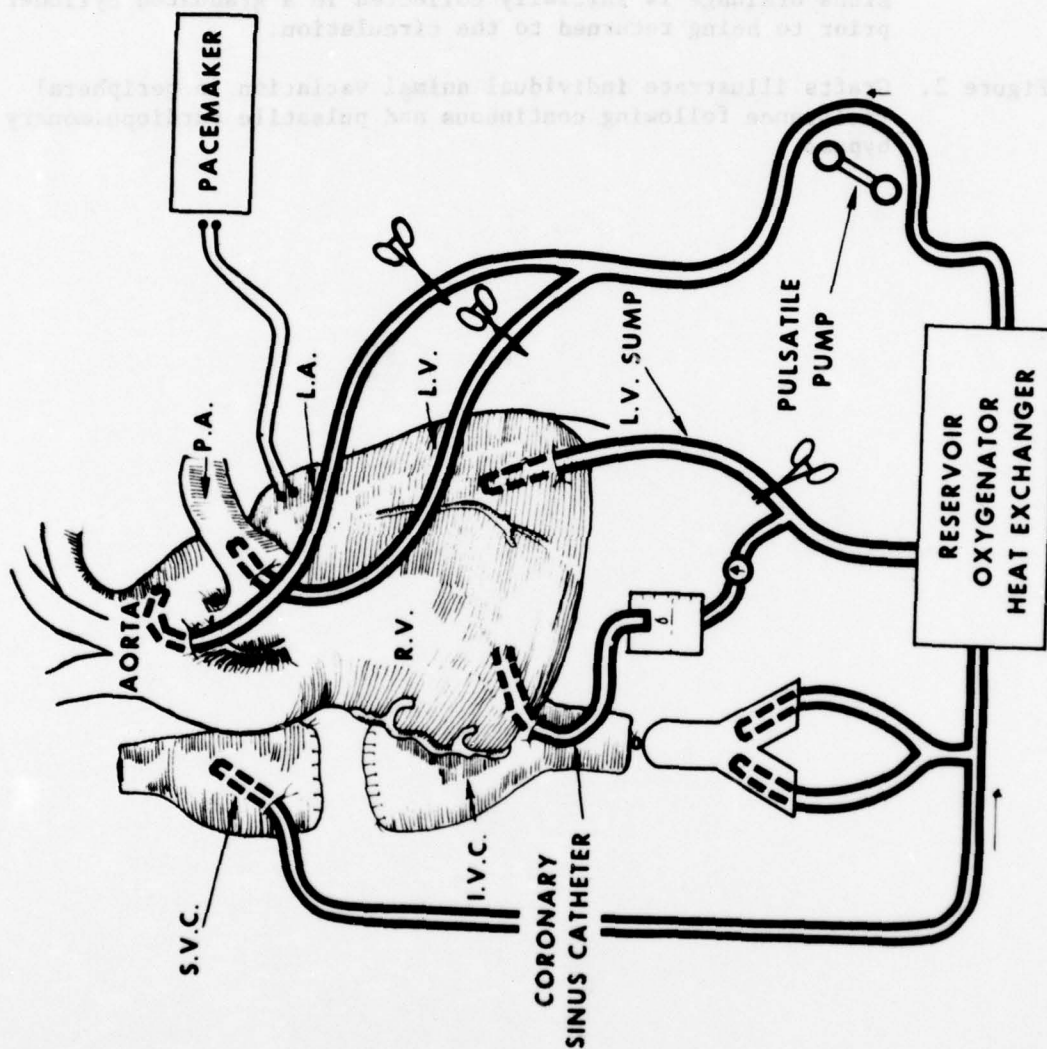
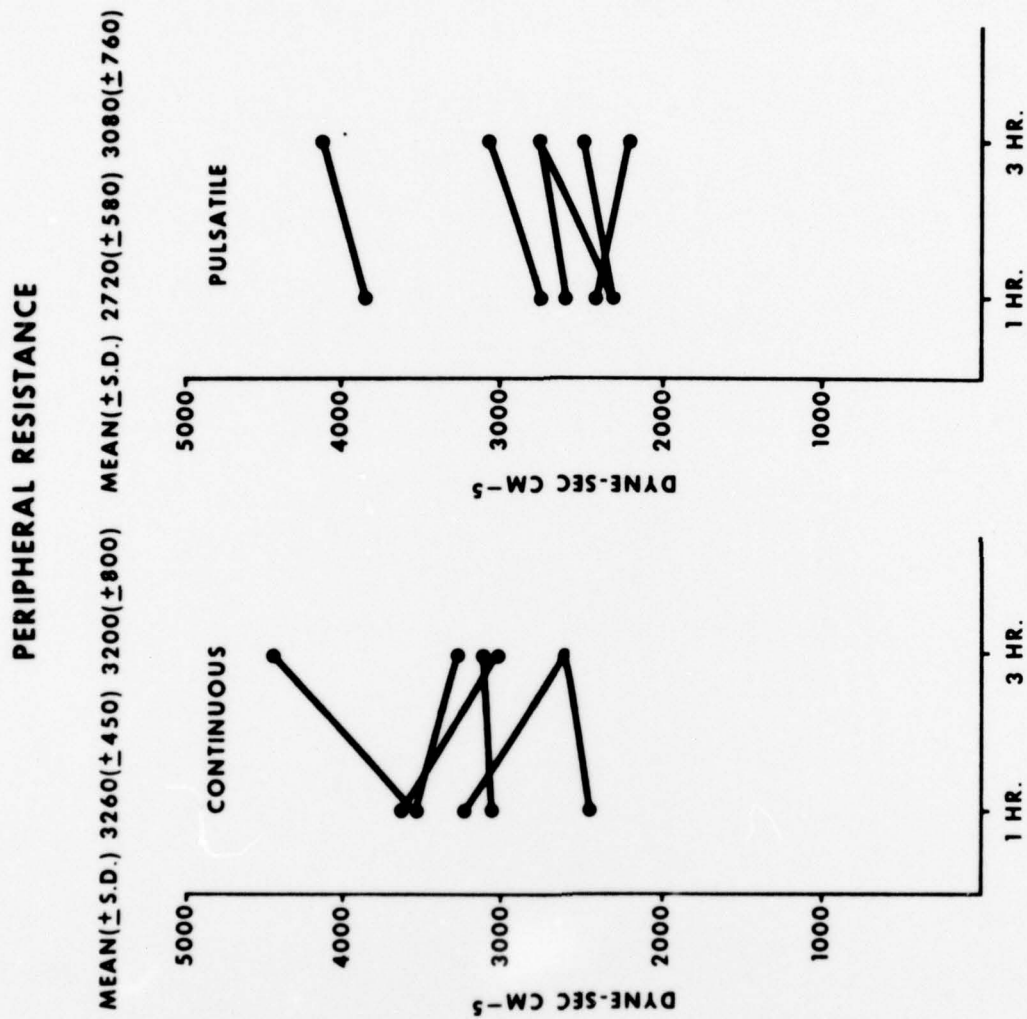


FIGURE 2



#### TITLES OF TABLES

- Table 1. Comparison between treatment groups for weight, hemoglobin, arterial pH, and arterial  $PO_2$  (values as mean  $\pm$  S.D.).
- Table 2. Comparison between treatment groups for stroke volume, stroke work, dp/dt Max, and mean arterial pressure ( $\bar{P}_a$ ) (values as mean  $\pm$  S.D.).
- Table 3. Comparison between treatment groups for coronary flow, myocardial oxygen consumption ( $MVO_2$ ), arterial-venous oxygen difference ( $S_{(a-v)}O_2$ ), and myocardial lactate extraction (values as mean  $\pm$  S.D.).
- Table 4. Comparison between treatment groups for total body oxygen consumption, venous lactate, venous pyruvate, venous lactate/pyruvate, and peripheral resistance (values as mean  $\pm$  S.D.).

APPENDIX B

TABLE 1

Comparison Between Treatment Groups  
for Weight, Hemoglobin, Arterial pH, and Arterial PO<sub>2</sub>\*

<u>Factors</u>	<u>Continuous (n=6)</u>		<u>Pulsatile (n=6)</u>	
	<u>Control</u>	<u>Test</u>	<u>Control</u>	<u>Test</u>
Weight (kg)	28(±2.5)		27(±2.2)	
Hemoglobin gm/dl	11.1(±1.5)	9.6(±1.9)	10.7(±2.2)	9.6(±2.3)
Arterial pH	7.30(±0.06) <sup>†</sup>	7.36(±0.05)	7.41(±0.04)	7.41(±0.03)
Arterial PO <sub>2</sub>	112(±33) <sup>†</sup>	207(±104)	164(±97)	280(±100)

\*Values as mean ± S.D.

<sup>†</sup>p<0.05



TABLE 2

Comparison Between Treatment Groups for Stroke Volume,  
Stroke Work, dp/dt Max, and Mean Arterial Pressure ( $\bar{P}_a$ )\*

<u>Factors</u>	<u>Continuous (n=6)</u>		<u>Pulsatile (n=6)</u>	
	<u>Control</u>	<u>Test</u>	<u>Control</u>	<u>Test</u>
Stroke volume(cc) (6mm LVEDP) % of control	26.7( $\pm$ 3.1)	24.2( $\pm$ 7.7) 90%	27.3( $\pm$ 4.7)	22.7( $\pm$ 1.9) 83%
Stroke work(gm-M) (6mm LVEDP) % of control	4.9( $\pm$ 2.5)	3.6( $\pm$ 1.6) 73%	4.7( $\pm$ 1.1)	3.7( $\pm$ 0.7) 78%
dp/dt Max(mmHg/sec) (100mm $\bar{P}_a$ ) % of control	5300( $\pm$ 3460)	5340( $\pm$ 3240) 101%	4480( $\pm$ 2180)	4260( $\pm$ 2010) 95%
$\bar{P}_a$ (mmHg) (6mm LVEDP) % of control	100( $\pm$ 18)	98( $\pm$ 29) 98%	88( $\pm$ 22)	92( $\pm$ 17) 105%

\*Values as mean  $\pm$  S.D.

TABLE 3

Comparison Between Treatment Groups for Coronary Flow,  
Myocardial Oxygen Consumption ( $\dot{M}V\dot{O}_2$ ), Arterial-Venous Oxygen  
Difference ( $S_{(a-v)}O_2$ ), and Myocardial Lactate Extraction\*

<u>Factors</u>	<u>Continuous (n=6)</u>		<u>Pulsatile (n=6)</u>	
	<u>Control</u>	<u>Test</u>	<u>Control</u>	<u>Test</u>
Coronary flow (cc/min)	121( $\pm$ 43)	108( $\pm$ 31)	108( $\pm$ 31)	95( $\pm$ 33)
% of control		89%		88%
$S_{(a-v)}O_2$	29( $\pm$ 9)	35( $\pm$ 13)	29( $\pm$ 10)	32( $\pm$ 12)
% of control		121%		110%
$\dot{M}V\dot{O}_2$ (cc/min)	5.2( $\pm$ 2.4)	5.3( $\pm$ 3.5)	4.1( $\pm$ 1.9)	3.2( $\pm$ 1.6)
% of control		102%		78%
Lactate Extraction (%)	3( $\pm$ 9%)	9( $\pm$ 9%)	8( $\pm$ 4%)	21( $\pm$ 21%)

\*Values as mean  $\pm$  S.D.

TABLE 4

Comparison Between Treatment Groups for Total Body  
Oxygen Consumption, Venous Lactate, Venous Pyruvate,  
Venous Lactate/Pyruvate, and Peripheral Resistance\*

<u>Factors</u>	Continuous (n=6)		Pulsatile (n=6)	
	<u>Control</u>	<u>Test</u>	<u>Control</u>	<u>Test</u>
Oxygen consumption (cc/min)	130(±59)	115(±51)	90(±38)	103(±31)
% of control		88%		114%
Venous lactate (mg/dl)	73.6(±19.5)	81.5(±32.1)	54.6(±10.0)	68.7(±21.8)
% of control		111%		126%
Venous pyruvate (mg/dl)	2.31(±4.8)	2.21(±0.57)	1.45(±0.56)	2.02(±4.4)
% of control		96%		139%
Lactate pyruvate % of control	31.3(±6.4)	37.2(±12.7)	20.0(±10.3)	35.3(±12.3)
		119%		118%
Peripheral resistance (dyne-sec cm <sup>-5</sup> )	3261(±447)	3199(±798)	2722(±583)	3078(±756)
% of control		98%		113%

\*Values as mean ± S.D.

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